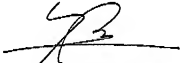
Verification of Accuracy of Translation

I, Yoichi INOUE, a national of Japan, c/o Asamura Patent Office, p.c. of 331-340, New Ohtemachi Building, 2-1, Ohtemachi-2-chome, Chiyoda-ku, Tokyo, Japan, am a Japanese patent attorney and do hereby solemnly and sincerely declare:

1) THAT I am well acquainted with the Japanese language and English language, and

2) THAT the attached is a full, true, accurate and faithful translation into the English language made by me of Japanese Patent Application No. 2002-379003 filed with the Japan Patent Office on December 27, 2002.

Signed this 30th day of October, 2009



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[Document] Specification
[Title of Invention] Pharmaceutical composition
[Claims]
1. A pharmaceutical composition comprising (1) aripiprazole and (2) a serotonin reuptake inhibitor.

2. The pharmaceutical composition of Claim 1 comprising (1) aripiprazole and (2) at least one selected from the group consisting of fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, or sertraline, or a salt thereof.

3. The pharmaceutical composition of Claim 2 comprising (1) aripiprazole and (2) citalopram.

4. The pharmaceutical composition of any one of Claims 1 to 3, comprising at least one pharmaceutically acceptable carrier.

5. The pharmaceutical composition of any one of Claims 1 to 4, wherein the pharmaceutical composition is a mood disorder treating agent.

6 The pharmaceutical composition of Claim 5, wherein the mood disorder is depression.

[Detailed Explanation of the Invention]
[0001]
[Technical field embracing the invention]
The present invention relates to a pharmaceutical composition. More specifically, the present invention relates to a pharmaceutical composition comprising aripiprazole.
[0002]
[Conventional art]
Aripiprazole, the general name 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydro-2(1H)-quinolinone, is a compound useful as an effective ingredient of an agent for treating schizophrenia (Patent publication 1). Aripiprazole is known to possess 5-HT_{1A} receptor agonist activity, and is known to be useful for types of depression and refractory depression, such as endogenous depression, major depression, melancholia and the like (Patent publication 2).

[0003]

The number of people with mood disorders such as depressive symptoms, depression, and exhibiting various symptoms of depression is continuously increasing every year for numerous reasons such as social stress. In Japan the occurrence rate of depression in the generation older than 65 years is 5% or more; mood disorders such as depressive symptoms, depression are psychotic disorders typical for old ages along with dementia disorders or neurosis. Many depressed patients show high recurrence rate, and severe depressive symptoms are major causes of suicide and drug abuse (Non-patent publication 1).

[0004]

Since the period of 1950, tricyclic antidepressant drugs (e.g., imipramine, desipramine, amitriptyline, etc.) have been developed that act to inhibit monoamine reuptake. They are frequently used for treating patients suffering from mood disorders, such as major depressive disorder. However, these drugs have side-effects, such as the following: dry mouth, hazy eyes, dysuria, constipation, recognition disturbance and the like due to anticholinergic activity; cardiovascular side-effects such as, orthostatic hypotension, tachycardia and the like on the basis of α_1-adrenoreceptor antagonist activity; side-effects such as, sedation, increase in the body weight and the like on the basis of histamine-H_1 receptor antagonist activity.

[0005]

In addition, since 1980s, serotonin reuptake inhibitors have been developed, including but not limited to fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, and sertraline, and these inhibitors have side-effects such as recognition disturbance, sleep disturbance, and exacerbation of anxiety and agitation as well as other side effects in the digestive organs, such as nausea, vomiting and the like.

[0006]

Because the mood disorders such as depressive symptoms, depression and the like are diseases with severely strong psychalgalia, the manifestation of new symptoms on the basis of these side-effects are quite serious problems in the therapy of mood disorders (Non-patent publication 2, Non-patent publication 3).

[0007]

Although the mood disorders such as major depressive symptoms, depression very are heterogeneous diseases, and the causes of these diseases have not fully been understood, it is likely that the abnormalities of the monoaminergic

central nervous system caused by serotonin, norepinephrine and dopamine and the like, and the abnormality of various hormones and peptides as well as various stressors are causes of depression and various mood disorders (Non-patent publication 4). For these reasons, even though antidepressant drugs, such as tricyclic antidepressants and serotonin reuptake inhibitors have been used, these drugs are not always effective in treating all depressed patients. About 30% of the depressed patients do not respond to the primarily selected antidepressants (Non-patent publication 5). Further, when a second or third antidepressant is administered to these patients, insufficient improvement of the symptoms occurs in about 10% of these patients (Non-patent publication 6). These patients are called refractory depression patients.

[0008]

In some cases, electric shock therapy is used to treat refractory depression, and the efficacy of this treatment has been reported. However, in fact, the condition of numerous patients is not improved (Non-patent publication 7). Additionally, psychological anguish experienced by these patients and their families concerning the use of the electric shock therapy can be severe.

[0009]

At present, as new therapeutic trials, combined therapies using an atypical antipsychotic drug, such as olanzepine, which is an agent for treating schizophrenia (anti-psychotic drug), together with an antidepressant drug such as serotonin reuptake inhibitor are proposed (Patent publication 3, Patent publication 4, Patent publication 5 and Patent publication 6). The purpose of conducting those combined therapies is to generate excellent effectiveness of the drugs, placing as the scientific ground on depression being a heterogenous disorder as mentioned above. Namely, said idea is such that a drug having new another pharmacological function is necessary for improving symptoms which cannot be treated with the pharmacological function of the administered drugs. These combined therapies to some extent improved the treatment effects but the treatment effects are still not satisfactory.

[0010]

Furthermore, conventional atypical antipsychotic drugs have significant problems relating to their safety. For example, clozapine, olanzapine and quetiapine have a strong body-weight increasing function and enhance the risk of diabetes mellitus (Non-patent publication 8, Non-patent publication 9). In fact, urgent safety alerts have been issued in Japan relating to hyperglycemia, diabetic

ketoacidosis and diabetic coma caused by olanzapine and quetiapine, indicating that these drugs were subjected to dosage contraindication to the patients with diabetes mellitus and patients having anamnesis of diabetes mellitus. Risperidone causes increases serum prolactin levels and produces extrapyramidal side effects at high dosages. Ziprasidone enhances the risk of severe arrhythmia on the basis of cardio-QTc prolongation action. Further, clozapine induces agranulocytosis, so that clinical use thereof is strictly restricted (Non-patent publication 10).

[0011]

[PATENT PUBLICATION 1]

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[0027]
[Problems to be solved by the present invention]

It is an object of the present invention to provide a pharmaceutical composition useful for treating a mood disorder.

[0028]
[Means to solve the problem]

The present inventors, as the result of intensive research aiming at solving the above mentioned problems, have found out that, by combining aripiprazole and a serotonin reuptake inhibitor, a mood disorder can effectively be treated. The present invention has been completed based on such knowledge.

1. The present invention is a pharmaceutical composition comprising (1) aripiprazole and (2) a serotonin reuptake inhibitor.

2. The present invention is the pharmaceutical composition described in item 1 above, comprising (1) aripiprazole and (2) at least one selected from the group consisting of fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, or sertraline, or a salt thereof.

3. The present invention is the pharmaceutical composition described in item 2 above, comprising (1) aripiprazole and (2) citalopram.

4. The present invention is the pharmaceutical composition described in item 2 above, comprising at least one pharmaceutically acceptable carrier.

5. The present invention is the pharmaceutical composition described in any one of items 1 to 4 above, wherein the pharmaceutical composition is a mood disorder treating agent.

6. The present invention is the pharmaceutical composition described in item 5 above, wherein the mood disorder is depression.

7. The present invention is a method of treating a mood disorder characterized in that (1) aripiprazole and (2) a serotonin reuptake inhibitor are co-used.

8. The present invention is the method described in item 7 above, wehrein (1) aripiprazole and (2) at least one selected from the group consisting of fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, or sertraline, or a salt thereof are co-used.

9. The present invention is the method described in item 8 above, wherein (1) aripiprazole and (2) citalopram are co-used.

10. The present invention is the method described in any one of items 7 to 9 above, wherein the mood disorder is depression.

[0029]

[Embodiment of carrying out the invention]

The present inventive pharmaceutical composition comprises (1) aripiprazole (first ingredient) and (2) a serotonin reuptake inhibitor (fsecond ingredient).

[0030]

First ingredient

Aripiprazole is an antipsychotic drug having new mechanism of action which is different from that of other atypical antipsychotic drugs. The available typical and atypical antipsychotic drugs act as antagonists at the dopamine-D_2 receptors. In contrast, aripiprazole acts as a partial agonist at the dopamine D_2 receptor (By Ishigooka Jyunya and Inada Ken: RINSHO SEISHIN YAKURI, Vol. 4, pp 1653-1664, (2001); Burris, K. D. et al.: J. Pharmacol. Exp. Ther., 302, pp 381-389, (2002)). In addition to the partial agonist action at dopamine-D_2 receptors, aripiprazole has activity as a partial agonist at the serotonin 5-HT_{1A} receptor, as well as antagonist action serotonin 5-HT_{2A} receptors. Accordingly, aripiprazole is a drug belonging to new category defined as a dopamine-serotonin system stabilizer (dopamine-serotonin nervous system stabilizer (Burris, K. D. et al., J. Pharmacol, Exp. Ther., 302, pp 381-389, 2002; Jordan, S. et al., Eur. J. Pharmacol. 441, pp 137-140, 2002).

[0031]

Aripiprazole to be used in the present invention may be any of form, for example, free bases, polymorphisms of every type of crystal, hydrate, salt (acid addition salts, etc.) and the like. Among of these forms, aripiprazole anhydride crystals B is a preferred form.

[0032]

As to method for preparing the aripiprazole anhydride crystals B, for example it is prepared by heating aripiprazole hydrate A as follows.

[0033]

Aripiprazole Hydrate A

The aripiprazole hydrate A having the physicochemical properties shown in (1) - (5) as follows:

[0034]

(1) It has an endothermic curve which is substantially identical to the thermogravimetric/differential thermal analysis (heating rate 5°C/min) endothermic curve shown in Figure 1. Specifically, it is characterized by the appearance of a small peak at about 71°C and a gradual endothermic peak around 60°C to 120°C.

[0035]

(2) It has an ^{1}H-NMR spectrum which is substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 2. Specifically, it has characteristic peaks at 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J = 7.4 Hz, 2H), 2.97 ppm (brt, J = 4.6 Hz, 4H), 3.92 ppm (t, J = 6.3 Hz, 2H), 6.43 ppm (d, J = 2.4 Hz, 1H), 6.49 ppm (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.04 ppm (d, J = 8.1 Hz, 1H), 7.11-7.17 ppm (m, 1H), 7.28-7.32 ppm (m, 2H) and 10.00 ppm (s, 1H).

[0036]

(3) It has a powder x-ray diffraction spectrum which is substantially identical to the powder x-ray diffraction spectrum shown in Figure 3. Specifically, it has characteristic peaks at 2θ = 12.6°, 15.4°, 17.3°, 18.0°, 18.6°, 22.5° and 24.8°.

[0037]

(4) It has clear infrared absorption bands at 2951, 2822, 1692, 1577, 1447, 1378, 1187, 963 and 784 cm^{-1} on the IR (KBr) spectrum.

[0038]

(5) It has a mean particle size of 50 μm or less.

[0039]

Method for preparing Aripiprazole Hydrate A

Aripiprazole hydrate A is prepared by milling conventional aripiprazole hydrate. Conventional milling methods can be used to mill conventional aripiprazole hydrate. For example, conventional aripiprazole hydrate can be milled in a milling machine. A widely used milling machine such as an atomizer, pin mill, jet mill or ball mill can be used. Among of these, the atomizer is preferably used.

[0040]

Regarding the specific milling conditions when using an atomizer, a rotational speed of 5000-15000 rpm could be used for the main axis, for example, with a feed rotation of 10-30 rpm and a screen hole size of 1-5 mm.

[0041]

The mean particle size of the aripiprazole hydrate A obtained by milling may be normally 50 μm or less, preferably 30 μm or less. Mean particle size can be ascertained by the particle size measuring method described hereinafter.

[0042]

Aripiprazole Anhydride Crystals B

Aripiprazole anhydride crystals B of the present invention have the physicochemical properties given in (6)-(10) below.

[0043]

(6) They have an ^{1}H-NMR spectrum which is substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 4. Specifically, they have characteristic peaks at 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J = 7.4 Hz, 2H), 2.97 ppm (brt, J = 4.6 Hz, 4H), 3.92 ppm (t, J = 6.3 Hz, 2H), 6.43 ppm (d, J = 2.4 Hz, 1H), 6.49 ppm (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.04 ppm (d, J = 8.1 Hz, 1H), 7.11-7.17 ppm (m, 1H), 7.28-7.32 ppm (m, 2H) and 10.00 ppm (s, 1H).

[0044]

(7) They have a powder x-ray diffraction spectrum which is substantially identical to the powder x-ray diffraction spectrum shown in Figure 5. Specifically, they have characteristic peaks at 2θ = 11.0°, 16.6°, 19.3°, 20.3° and 22.1°.

[0045]

(8) They have clear infrared absorption bands at 2945, 2812, 1678, 1627, 1448, 1377, 1173, 960 and 779 cm^{-1} on the IR (KBr) spectrum.

[0046]

(9) They exhibit an endothermic peak near about 141.5°C in thermogravimetric/differential thermal analysis (heating rate 5°C/min).

[0047]

(10) They exhibit an endothermic peak near about 140.7°C in differential scanning calorimetry (heating rate 5°C/min).

[0048]

When the small particle size is required for solid preparation, such as tablets and other solid dose formulations including for example flash melt formulations, the mean particle size is preferably 50 μm or less.

[0049]

Method for manufacturing Aripiprazole Anhydride Crystals B

The aripiprazole anhydride crystals B of the present invention are manufactured, for example, by heating the aforementioned aripiprazole hydrate A at 90-125°C. The heating time is generally about 3-50 hours, but cannot be stated unconditionally, because it differs depending on heating temperature. The heating time and heating temperature are inversely related, so that for example when the heating time is longer, then the heating temperature is lower, and when the heating temperature is higher then the heating time is shorter. Specifically, if the heating temperature of aripiprazole hydrate A is 100°C, the heating time may be 18 hours or

more, or preferably about 24 hours. If the heating temperature of aripiprazole hydrate A is 120°C, on the other hand, the heating time may be about 3 hours. The aripiprazole anhydride crystals B of the present invention can be prepared with certainty by heating aripiprazole hydrate A for about 18 hours at 100°C, and then heating it for about 3 hours at 120°C. The aripiprazole anhydride crystals B of the present invention can also be obtained if the heating time is extended still further, but this method may not be economical.

[0050]

When small particle size is not required for the formulation, e.g., when drug substance is being prepared for injectable or oral solution formulations, aripiprazole anhydride crystals B can be also obtained by the following process.

[0051]

Aripiprazole anhydride crystals B of the present invention are prepared for example by heating conventional aripiprazole anhydride crystals at 90-125°C. The heating time is generally about 3-50 hours, but cannot be stated unconditionally because it differs depending on heating temperature. The heating time and heating temperature are inversely related, so that for example if the heating time is longer, the heating temperature is lower, and if the heating time is shorter, the heating temperature is higher. Specifically, if the heating temperature of the aripiprazole anhydride crystals is 100°C, the heating time may be about 4 hours, and if the heating temperature is 120°C the heating time may be about 3 hours.

[0052]

Furthermore, aripiprazole anhydride crystals B of the present invention are prepared for example, by heating conventional aripiprazole hydrate at 90-125°C. The heating time is generally about 3-50 hours, but cannot be stated unconditionally because it differs depending on heating temperature. The heating time and heating temperature are inversely related, so that for example, if the heating time is longer, the heating temperature is lower, and if the heating time is shorter, the heating temperature is higher. Specifically, if the heating temperature of the aripiprazole hydrate is 100°C, the heating time may be about 24 hours, and if the heating temperature is 120°C the heating time may be about 3 hours.

[0053]

The aripiprazole anhydride crystals which are the raw material for preparing the aripiprazole anhydride crystals B of the present invention are prepared for example by Method a or b below.

[0054]

"Method a": Process for preparing crude crystals of Aripiprazole

Conventional aripiprazole anhydride crystals are prepared by well-known methods, as described in Example 1 of Japanese Unexamined Patent Publication No. 191256/1990.

7-(4-bromobutoxy)-3,4-dihydrocarbostyril, is reacted with 1-(2,3-dichlorophenyl)piperazine and the thus obtained crude aripiprazole crystals are re-crystallized from ethanol.

[0055]

"Method b": Process for preparing conventional Aripiprazole Anhydride

The Method b is described in the Proceedings of the 4th Joint Japanese-Korean Symposium on Separation Technology (October 6-8, 1996).

[0056]

The aripiprazole hydrate which is the raw material for preparing the aripiprazole anhydride crystals B of the present invention is prepared for example by Method c below.

[0057]

"Method c": Method for preparing conventional Aripiprazole Hydrate

Aripiprazole hydrate is easily obtained by dissolving the aripiprazole anhydride crystals obtained by Method a above in a hydrous solvent, and heating and then cooling the resulting solution. Using this method, aripiprazole hydrate is precipitated as crystals in the hydrous solvent.

[0058]

An organic solvent containing water is usually used as the hydrous solvent. The organic solvent may be preferable one which is miscible with water, for example an alcohol such as methanol, ethanol, propanol or isopropanol, a ketone such as acetone, an ether such as tetrahydrofuran, dimethylformamide, or a mixture thereof, ethanol is particularly desirable. The amount of water in the hydrous solvent may be 10-25% by volume of the solvent, or preferably close to 20% by volume.

[0059]

Aripiprazole can easily form an acid addition salt with a pharmaceutically acceptable acid. As to such acid, for example, an inorganic acid, such as sulfuric acid, nitric acid, hydrochloric acid, phosphoric acid, hydrobromic acid, etc.; an organic acid such as, acetic acid, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid, etc. can be exemplified. Similar to aripiprazole of

free forms, these acid addition salts can also be used as the active ingredient compounds in the present invention.

[0060]

The objective compound thus obtained through each one of production steps, is separated from the reaction system by usual separation means, and can be further purified. As to the separation and purification means, for example, distillation method, solvent extraction method, dilution method, re-crystallization method, column chromatography, ion-exchange chromatography, gel chromatography, affinity chromatography, preparative thin-layer chromatography and the like can be exemplified.

[0061]

Second ingredient

In the composition of the present invention, a serotonin reuptake inhibitor is used as the second ingredient.

[0062]

Compounds which function as serotonin reuptake inhibitors can be widely used as the serotonin reuptake inhibitors and are known to one of ordinary skill in the art.

[0063]

Among the serotonin reuptake inhibitors, those having IC_{50} value (a concentration of the drug that inhibit serotonin reuptake by about 50%), measured by the method of Wong et al. (Neuropsychopharmacology, 8, pp 337-344 (1993)), the standard pharmacological assay method, is about 1000 nM or lower are preferable.

[0064]

As to such serotonin reuptake inhibitors, for example, fluvoxamine (5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone-O-(2-aminoethyl)oxime), fluoxetine (N-methyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine), paroxetine (trans-(-)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine), sertraline (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylylamine hydrochloride), venlafaxine, milnacipran (N,N-diethyl-2-aminomethyl-1-phenylcyclopropanecarboxyamide), citalopram, and the like may be used.

[0065]

The serotonin reuptake inhibitor may be either in the form of a free base or a salt (an acid addition salt or the like). Further, the serotonin reuptake inhibitor may be either a racemic modifications or R and S enantiomers.

[0066]

The serotonin reuptake inhibitors may be either a single use of one serotonin reuptake inhibitor, and in case of need, two or more of the serotonin reuptake inhibitors may be used in combination. Use of one serotonin reuptake inhibitor is preferred.

[0067]

The serotonin reuptake inhibitor can easily form an acid addition salt with a pharmaceutically acceptable acid. As to such acid, for example, an inorganic acid, such as sulfuric acid, nitric acid, hydrochloric acid, phosphoric acid, hydrobromic acid, etc.; an organic acid such as, acetic acid, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid, etc. can be exemplified. Similar to the reuptake inhibitor of free forms, these acid addition salts can also be used as the active ingredient compounds in the present invention.

[0068]

Among the serotonin reuptake inhibitors, a compound having an acidic group can easily form salt by reacting with a pharmaceutically acceptable basic compound. As to such basic compound, a metal hydroxide, for example, sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide and the like; an alkali metal carbonate or bicarbonate, for example sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and the like; a metal alcoholate, for example sodium methylate, potassium ethylate and the like can be exemplified.

[0069]

The thus obtained salt form of serotonin reuptake inhibitor is separated from the reaction system by usual separation means, and can be further purified. As to the separation and purification means, for example, distillation method, solvent extraction method, dilution method, recrystallization method, column chromatography, ion-exchange chromatography, gel chromatography, affinity chromatography, preparative thin-layer chromatography and the like can be exemplified.

[0070]

Combination of the first ingredient with the second ingredient

As to combination of carbostyril derivatives with activity as dopamine-serotonin stabilizers, non-limiting examples of aripiprazole and dehydroaripiprazole are described herein. When aripiprazole is combined with at

least one serotonin reuptake inhibitor, the following are non-limiting examples of such combinations: aripiprazole/fluoxetine, aripiprazole/duloxetine, aripiprazole/venlafaxine, aripiprazole/milnacipran, aripiprazole/citalopram, aripiprazole/fluvoxamine, aripiprazole/paroxetine, and aripiprazole/sertraline A preferred embodiment comprises a combination of aripiprazole/citalopram.

[0071]

Dosage of the drug used in the present invention is decided by considering the properties of each constituting drug to be combined, the properties of drugs after combination and symptoms of the patient (existence of other diseases beside the depression). General outlines of the dosage are provided in the following guidelines.

[0072]

Aripiprazole: generally about 0.1 to 100 mg/once a day (or about 0.05 to about 50 mg/twice a day), preferably about 1 to 30 mg/once a day (or about 0.5 to about 15 mg/twice a day).

Fluoxetine: generally about 1 to about 80 mg/once a day, preferably about 10 to about 40 mg/once a day;

Duloxetine: generally about 1 to 160 mg/once a day (or 80 mg/twice a day), preferably about 5 to about 20 mg/once a day;

Venlafaxine: generally about 10 to 150 mg/1 to 3 times a day, preferably about 25 to 125 mg/3 times a day;

Milnacipran: generally about 10 to 100 mg/1 to 2 times a day, preferably about 25 to about 50 mg/twice a day;

Citalopram: generally about 5 to about 50 mg/once a day, preferably about 10 to about 30 mg/once a day;

Fluvoxamine: generally about 20 to 500 mg/once a day, preferably about 50 to 300 mg/once a day;

Paroxetine: generally about 20 to about 50 mg/once a day, preferably about 20 to about 30 mg/once a day; or,

Sertraline: generally, about 20 to about 500 mg/once a day, preferably about 50 to about 200 mg/once a day.

Generally, the weight ratio of the first ingredient to the second ingredient is selected in accordance with the above-mentioned guideline. As to the ratio of the first ingredient and the second ingredient, if the first ingredient is about 1 part by weight of the former, the second ingredient is used at about 0.01 to about 500 parts by weight, preferably about 0.1 to about 100 parts by weight.

[0073]

Pharmaceutically acceptable carriers include diluents and excipients generally used in pharmaceutical preparations, such as fillers, extenders, binders, moisturizers, disintegrators, surfactant, and lubricants.

[0074]

The pharmaceutical composition of the present invention may be formulated as an ordinary pharmaceutical preparation, for example in the form of tablets, flash melt tablets, pills, powder, liquid, suspension, emulsion, granules, capsules, suppositories or injection (liquid, suspension, etc.), troches, intranasal spray percutaneous patch and the like.

[0075]

In case of shaping to tablet formulation, a wide variety of carriers that are known in this field can be used. Examples include lactose, saccharose, sodium chloride, glucose, urea, starch, xylitol, mannitol, erythritol, sorbitol, calcium carbonate, kaolin, crystalline cellulose, silic acid and other excipients; water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, polyvinyl pyrrolidone and other binders; dried starch, sodium alginate, agar powder, laminaran powder, sodium hydrogencarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, stearic acid monoglyceride, starch, lactose and other disintegrators; white sugar, stearin, cacao butter, hydrogenated oil and other disintegration inhibitors; quaternary ammonium salt, sodium lauryl sulfate and other absorption accelerator; glycerine, starch and other moisture retainers; starch, lactose, kaolin, bentonite, colloidal silic acid and other adsorbents; and refined talc, stearate, boric acid powder, polyethylene glycol and other lubricants and the like. Tablets can also be formulated if necessary as tablets with ordinary coatings, such as sugar-coated tablets, gelatin-coated tablets, enteric coated tablets and film coated tablets, as well as double tablets and multilayered tablets.

[0076]

In case of shaping to pills, a wide variety of carriers that are known in this field can be used. Examples include glucose, lactose, starch, cacao butter, hardened vegetable oil, kaolin, talc and other excipients; gum arabic powder, traganth powder, gelatin, ethanol and other binders; and laminaran, agar and other disintegrators and the like.

[0077]

In case of shaping to a suppository formulation, a wide variety of

carriers that are known in the field can be used. Examples include polyethylene glycol, cacao butter, higher alcohol, esters of higher alcohol, gelatin semi-synthetic glyceride and the like.

[0078]

Capsules are prepared according to ordinary methods by mixing aripiprazole anhydride crystals as the first ingredient and the second ingredient, and the various carriers described above and packing them in hard gelatin capsules, soft capsules hydroxypropylmethyl cellulose capsules (HPMC capsules) and the like.

[0079]

In addition, colorants, preservatives, perfumes, flavorings, sweeteners and the like as well as other drugs may be contained in the pharmaceutical composition.

[0080]

The amounts of the first ingredient and the second ingredient to be contained in the pharmaceutical composition of the present invention are suitably selected from a wide range depending on the diseases to be treated. Generally, about 1 to 70 parts by weight, preferably about 1 to 30 parts by weight of the first ingredient and the second ingredient in the total amount on the basis of the pharmaceutical composition.

[0081]

The methods for administration of the pharmaceutical composition of the present invention are not specifically restricted. The composition is administered depending on each type of preparation form, and the age, gender and other condition of the patient (degree and conditions of the disease, etc.). For example, tablets, pills, liquids, suspensions, emulsions, granules and capsules are administered orally. In case of injection preparation, it is administered intravenously either singly or mixed with a common auxiliary liquid such as solutions of glucose or amino acid. Further, if necessary, the injection preparation is singly administered intradermally, subcutaneously or intraperitoneally. In case of a suppository, it is administered intrarectally.

[0082]

Administration forms of the pharmaceutical composition of the present invention may be any type by which the effective levels of both aripiprazole and serotonin reuptake inhibitors can be provided in vivo at the same time. In one embodiment, aripiprazole together with a serotonin reuptake inhibitor are contained in one pharmaceutical composition and this composition may be administered. On

the other hand, each one of aripiprazole and a serotonin reuptake inhibitor are contained individually in a pharmaceutical preparation respectively, and each one of these preparations may be administered at the same time or at suitable intervals.

[0083]

Furthermore, the present invention provides a method of treating a mood disorder characterized in that (1) aripiprazole and (2) a serotonin reuptake inhibitor are co-use

[0084]

[Effect of the invention]

The present inventive pharmaceutical composition is extremely effective for treatment or improvement of depressive symptoms, depression, refractory depression.

[0085]

The present inventive pharmaceutical composition can express broader neurotransmission adjusting functions, providing a better influence on abnormal neurotransmission for more nerve systems.

[0086]

The present inventive pharmaceutical composition, having an excellent treatment or improvement effect, the dosage for treatment or improvement can be reduced; the result provides less side effects and excellent safety .

[0087]

The mood disorders which can be treated by the pharmaceutical composition of the present invention includes the mood disorders classified in "Diagnostic and Statistical Manual of Mental Disorders" Fourth Edition (DSM-IV) published by the American Psychiatric Association. These mood disorders include, for example, major depressive disorder, all mood disorders, schizoaffective disorder, dementia with depressive symptoms and the like. A preferred disorder to be treated with the present invention is major depressive disorder.

[0088]

The pharmaceutical composition of the present invention is useful for treating major depressive disorder, endogenous depression, melancholia, depression in combination with psychotic episodes, bipolar disorder with depressive phase, refractory depression, dementia of the Alzheimer's type with depressive symptoms, Parkinson's disease with depressive symptom, senile dementia, mood disorder associated with cerebral blood vessels and mood disorder following head injury and the like. In addition to the methods for treatment described herein, additional

disclosure for designing clinical studies is provided in J. Clin. Psychiatry, 2002, 63:(12):1164-70, J. Clin. Psychiatry, 2002, 63:(8):733-6, and J. Clin. Psychiatry, 2002, 63:(5): 391-5.

[0089]

[Examples]

The present invention will be explained more in detail by illustrating Reference Examples, Example and Formulation Sample Examples.

[0090]

First, analytical methods are explained.

[0091]

Analytical Methods

(1) The ^{1}H-NMR spectrum was measured in DMSO-d_6 by using TMS as the standard.

[0092]

(2) Powder X-ray Diffraction

By using RAD-2B diffraction meter manufactured by Rigaku Denki, the powder x-ray diffraction pattern was measured at room temperature by using a Cu Ka filled tube (35 kV 20mA) as the x-ray source with a wide-angle goniometer, a 1° scattering slit, an 0.15 mm light-intercepting slit, a graphite secondary monochromator and a scintillation counter. Data collection was done in 2θ continuous scan mode at a scan speed of 5°/minute in scan steps of 0.02° in the range of 3° to 40°.

[0093]

(3) The IR spectrum was measured by the KBr method.

[0094]

(4) Thermogravimetric/Differential Thermal Analysis

Thermogravimetric/differential thermal analysis was measured by using SSC 5200 control unit and TG/DTA 220 simultaneous differential thermal/ thermogravimetric measuring unit manufactured by Seiko Corp. Samples (5 – 10 mg) were placed in open aluminum pans and heated at from 20°C to 200°C in a dry nitrogen atmosphere at a heating rate of 5°C/minute. α-Alumina was used as the standard substance.

[0095]

(5) Differential Scanning Calorimetry

Thermogravimetric/differential thermal analysis was measured by using SSC 5200 control unit and DSC 220C differential scanning calorimeter

manufactured by Seiko Corp. Samples (5 – 10 mg) were placed in crimped aluminum pans and heated from 20°C to 200°C in a dry nitrogen atmosphere at a heating rate of 5°C/minute. α-Alumina was used as the standard substance.

[0096]

(6) Particle Size Measurement

The particles (0.1 g) to be measured were suspended in a 20 ml n-hexane solution of 0.5 g soy lecithin, and particle size was manufactured by using a size distribution measuring meter (Microtrack HRA, manufactured by Microtrack Co.).

[0097]

Reference Example 1

7-(4-Chlorobutoxy)-3,4-dihydrocarbostyril (19.4 g) and monohydrochloride 16.2 g of 1-(2,3-dichlorophenyl) piperadine 1 hydrochloride were added to a solution of 8.39 g of potassium carbonate dissolved in 140 ml of water, and refluxed for 3 hours under agitation. After the reaction was complete, the mixture was cooled and the precipitated crystals collected by filtration. These crystals were dissolved in 350 ml of ethyl acetate, and about 210 ml of water/ethyl acetate azeotrope was removed under reflux. The remaining solution was cooled, and the precipitated crystals were collected by filtration. The resulting crystals were dried at 60°C for 14 hours to obtain 20.4 g (74.2%) of crude product of aripiprazole.

[0098]

The crude product of aripiprazole (30 g) obtained above was re-crystallized from 450 ml of ethanol according to the methods described in Japanese Unexamined Patent Publication No. 191256/1990, and the resulting crystals were dried at 80°C for 40 hours to obtain aripiprazole anhydride crystals. The yield was 29.4 g (98.0%).

[0099]

The melting point (mp) of these aripiprazole anhydride crystals was 140°C, which is identical to the melting point of the aripiprazole anhydride crystals described in Japanese Unexamined Patent Publication No. 191256/1990.

[0100]

Reference Example 2

The crude product of aripiprazole (6930 g) obtained in Reference Example 1 was heat dissolved by heating in 138 liters of hydrous ethanol (water content 20% by volume) according to the method presented at the 4th Joint Japanese-Korean Symposium on Separation Technology, the solution was gradually

(2-3 hours) cooled to room temperature, and then was chilled to near 0°C. The precipitated crystals were collected by filtration, about 7200 g of aripiprazole hydrate (wet-state).

[0101]

The wet-state aripiprazole hydrate crystals obtained above were dried at 80°C for 30 hours to obtain 6480 g (93.5%) of aripiprazole hydrate crystals. The melting point (mp) of these crystals was 139.5°C.

[00102]

The water content of the crystals were confirmed by the Karl Fischer method, the moisture value was 0.03%, thus the crystals were confirmed as anhydrous product.

[0103]

Reference Example 3

The aripiprazole hydrate (820 g) in wet state obtained from Reference Example 2 was dried at 50°C for 2 hours to obtain 780 g of aripiprazole hydrate crystals. The moisture value of the crystals had a moisture value was 3.82% measured according to the Karl Fischer method. As shown in Figure 6, thermogravimetric/differential thermal analysis revealed endothermic peaks at 75.0, 123.5 and 140.5°C. Because dehydration began near at 70°C, there was no clear melting point (mp) was observed.

[0104]

As shown in Figure 7, the powder x-ray diffraction spectrum of aripiprazole hydrate obtained by this method exhibited characteristic peaks at $2\theta =$ 12.6°, 15.1°, 17.4°, 18.2°, 18.7°, 24.8° and 27.5°.

[0105]

The powder x-ray diffraction spectrum of this aripiprazole hydrate was identical to the powder x-ray diffraction spectrum of aripiprazole hydrate presented at the 4th Joint Japanese-Korean Symposium on Isolation Technology.

[0106]

Reference Example 4

The aripiprazole hydrate crystals (500.3 g) obtained in Reference Example 3 were milled by using a sample mill (small size atomizer). The main axis rotation rate was set to 12,000 rpm and the feed rotation rate to 17 rpm, and a 1.0 mm herringbone screen was used. Milling was finished in 3 minutes, and obtained 474.6 g (94.9%) of aripiprazole hydrate A.

[0107]

The aripiprazole hydrate A (powder) obtained in this way had a mean particle size of 20-25 μm. The melting point (mp) was undetermined because dehydration was observed beginning near at 70°C.

[0108]

The aripiprazole hydrate A (powder) obtained above exhibited an ^{1}H-NMR (DMSO-d_6, TMS) spectrum which was substantially identical to the ^{1}H-NMR spectrum shown in Figure 2. Specifically, it had characteristic peaks at 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J = 7.4 Hz, 2H), 2.97 ppm (brt, J = 4.6 Hz, 4H), 3.92 ppm (t, J = 6.3 Hz, 2H), 6.43 ppm (d, J = 2.4 Hz, 1H), 6.49 ppm (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.04 ppm (d, J = 8.1 Hz, 1H), 7.11-7.17 ppm (m, 1H), 7.28-7.32 ppm (m, 2H) and 10.00 ppm (s, 1H).

[0109]

The aripiprazole hydrate A (powder) obtained above had a powder x-ray diffraction spectrum which was substantially identical to the powder x-ray diffraction spectrum shown in Figure 3. Specifically, it had characteristic peaks at 2θ = 12.6°, 15.4°, 17.3°, 18.0°, 18.6°, 22.5° and 24.8°. This pattern is different from the powder x-ray spectrum of unmilled Aripiprazole hydrate shown in Figure 7.

[0110]

The aripiprazole hydrate A (powder) obtained above had infrared absorption bands at 2951, 2822, 1692, 1577, 1447, 1378, 1187, 963 and 784 cm^{-1} on the IR (KBr) spectrum.

[0111]

As shown in Figure 1, the aripiprazole hydrate A (powder) obtained above had a weak peak at 71.3°C in thermogravimetric/differential thermal analysis and a broad endothermic peak (weight loss observed corresponding to one molecule of water) between 60-120°C which was clearly different from the endothermic curve of unmilled aripiprazole hydrate (see Figure 6).

[0112]

Example 1

The aripiprazole hydrate A (powder) (44.29 kg) obtained in the Reference Examples was dried at 100°C for 24 hours by using a hot air dryer and further heated at 120°C for 3 hours, to obtain 42.46 kg (yield; 99.3 %) of aripiprazole anhydride Crystals B.

[0113]

These aripiprazole anhydride crystals B had a melting point (mp) of 139.7°C.

[0114]

The aripiprazole anhydride crystals B obtained above had an ^{1}H-NMR spectrum (DMSO-d_6, TMS) which was substantially identical to the ^{1}H-NMR spectrum shown in Figure 4. Specifically, they had characteristic peaks at 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J = 7.4 Hz, 2H), 2.97 ppm (brt, J = 4.6 Hz, 4H), 3.92 ppm (t, J = 6.3 Hz, 2H), 6.43 ppm (d, J = 2.4 Hz, 1H), 6.49 ppm (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.04 ppm (d, J = 8.1 Hz, 1H), 7.11-7.17 ppm (m, 1H), 7.28-7.32 ppm (m, 2H) and 10.00 ppm (s, 1H).

[0115]

The aripiprazole anhydride crystals B obtained above had a powder x-ray diffraction spectrum which was substantially the identical to the powder x-ray diffraction spectrum shown in Figure 5. Specifically, they had characteristic peaks at $2\theta = 11.0°$, 16.6°, 19.3°, 20.3° and 22.1°.

[0116]

The aripiprazole anhydride crystals B obtained above had remarkable infrared absorption bands at 2945, 2812, 1678, 1627, 1448, 1377, 1173, 960 and 779 cm^{-1} on the IR (KBr) spectrum.

[0117]

The aripiprazole anhydride crystals B obtained above exhibited an endothermic peak near about at 141.5°C in thermogravimetric/differential thermal analysis.

[0118]

The aripiprazole anhydride crystals B obtained above exhibited an endothermic peak near about at 140.7°C in differential scanning calorimetry.

[0119]

Pharmacological Test

The forced swimming test proposed by Porsolt et al. (Porsolt, R. D. et al.: Arch. Int. Pharmacodyn., 229, 327-336, 1977) is widely used as to a experimental animal model for predicting the antidepressant activity in clinical settings. In this experimental model, a test mouse is put in a cylinder in which a suitable amount of water is contained, and the antidepressant action of a test drug is detected by measuring the immobility time, as the indication, shown by the mouse. It was reported that the action of shortening the immobility time is correlated with clinically observed antidepressive action (Willner, P.: Psychopharmacology, 83: 1-16, 1984). The crisis of depression is closely concerned with lowering of serotonin

5-HT_{1A} receptor neurotransmission action, and the present inventors have found the facts that antidepressive action of antidepressants which affect the serotonin system can be detected more precisely using prolongation of the immobility time performed with WAY-100635, which is a selective serotonin 5-HT_{1A} receptor antagonist. The prolongation of the immobility time performed by WAY-100635 is defined as the indication. In this manner, the antidepressive action of test antidepressants was determined by taking the prolongation of immobility time performed by WAY-100635 in the forced swimming test as the indication.

[0120]

In a cylinder (diameter: 9 cm, height 20 cm), water is poured therein up to the height of 9.5 cm, from the bottom, then a mouse of ICR strain is placed in the cylinder. After placing the mouse in the cylinder, an immobility time of 6 minutes is measured. During the test, the water temperature is maintained at 23 to 24°C. A test drug is orally administered to the mouse at 1 or 2 hours before placing the mouse in the water. WAY-100635 is administered subcutaneously to the mouse 30 minutes before placing the mouse in the water.

[0121]

During this test, Aripiprazole is used in combination with Citalopram, Fluoxetine, Venlafaxine or Milnacipran. Following such combination administration, a decrease in the immobility time (the antidepressant activity) is observed in comparison with the case of single use of each one of Aripiprazole, Citalopram, Fluoxetine, Venlafaxine or Milnacipran, respectively.

[0122]

Further, when Aripiprazole is used in combination with Citalopram, Fluoxetine, Venlafaxine or Milnacipran, a decrease in the immobility time (the antidepressant activity) is observed in comparison to administration of the available atypical antipsychotic drugs such as Olanzapine, Quetiapine, Risperidone in combination with Citalopram, Fluoxetine, Venlafaxine or Milnacipran.

[0123]

Formulation Sample Example 1

Aripiprazole Anhydride Crystals B	5 mg
Fluoxetine	20 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	220 mg

According to a preparation method which is well-known to a person having an ordinary skill in the art, the tablet containing the above mentioned formulation was prepared.

[0124]

Formulation Sample Example 2

Aripiprazole Anhydride Crystals B	5 mg
Duloxetine	20 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	220 mg

According to a common method, the tablet containing the above mentioned formulation was prepared.

[0125]

Formulation Sample Example 3

Aripiprazole Anhydride Crystals B	5 mg
Venlafaxine	75 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	275 mg

According to a common method, the tablet containing the above mentioned formulation was prepared.

[0126]

Formulation Sample Example 4

Aripiprazole Anhydride Crystals B	5 mg
Milnacipran	50 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	250 mg

According to a common method, the tablet containing the above mentioned formulation was prepared.

[0127]

Formulation Sample Example 5

Aripiprazole Anhydride Crystals B	5 mg
Citalopram	20 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	220 mg

According to a common method, the tablet containing the above mentioned formulation was prepared.

[0128]

Formulation Sample Example 6

Aripiprazole Anhydride Crystals B	5 mg
Fluvoxamine	50 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	250 mg

According to a common method, the tablet containing the above mentioned formulation was prepared.

[0129]

Formulation Sample Example 7

Aripiprazole Anhydride Crystals B	5 mg
Paroxetine	20 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	220 mg

According to a common method, the tablet containing the above mentioned formulation was prepared.

[0130]

Formulation Sample Example 8	
Aripiprazole Anhydride Crystals B	5 mg
Sertraline	50 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	250 mg

According to a common method, the tablet containing the above mentioned formulation was prepared.

[Brief description of the drawings]

Brief description of the drawings

[Figure 1] The thermogravimetric/differential thermogram of the aripiprazole hydrate A obtained in Reference Example 4.

[Figure 2 he ^{1}H-NMR spectrum (DMSO-d_6, TMS) of the aripiprazole hydrate A obtained in Reference Example 4.

[Figure 3] The powder X-ray diffraction diagram of the aripiprazole hydrate A obtained in Reference Example 4.

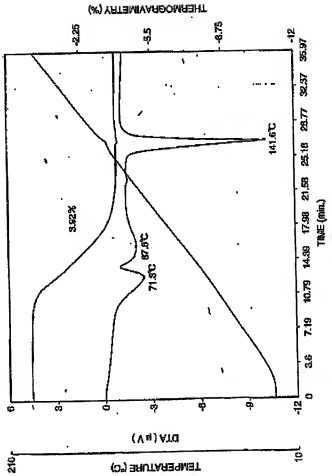
[Figure 4] The ^{1}H-NMR spectrum (DMSO-d_6, TMS) of the aripiprazole anhydride crystals B obtained in Example 1.

[Figure 5] The powder X-ray diffraction diagram of the aripiprazole anhydride crystals B obtained in Example 1.

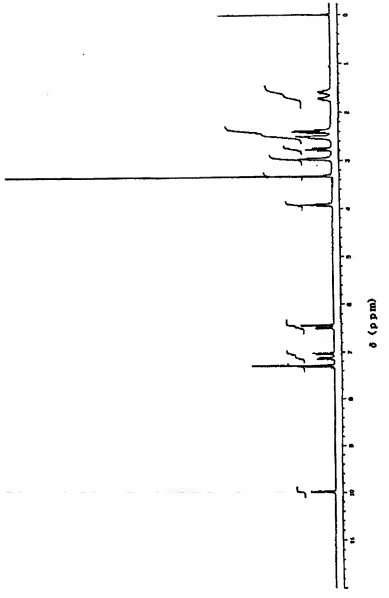
[Figure 6] The thermogravimetric/differential thermogram of the aripiprazole hydrate A obtained in Reference Example 3.

[Figure 7] The powder X-ray diffraction diagram of aripiprazole hydrate obtained in Reference Example 3.

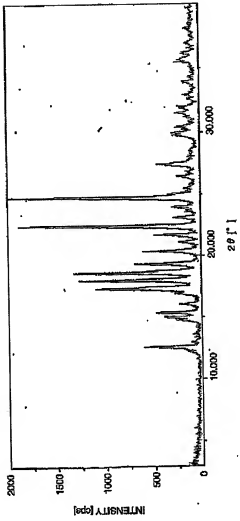
[Document] Drawings
[Figure 1]



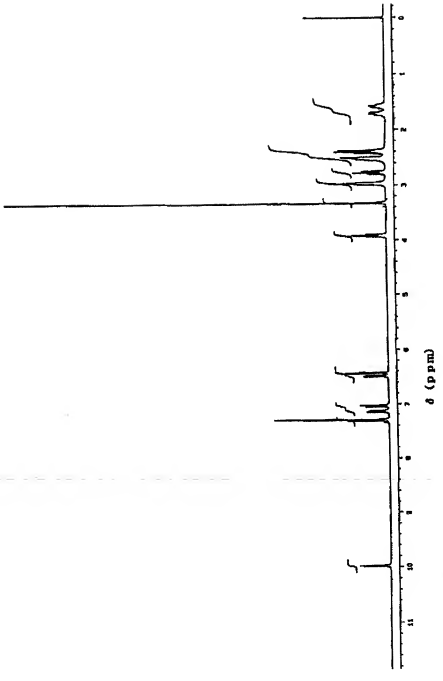
[Figure 2]



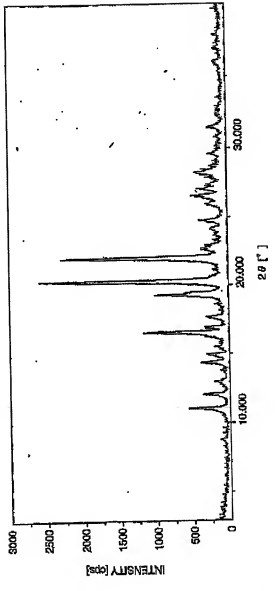
[Figure 3]



[Figure 4]



[Figure 5]


INTENSITY [cps]
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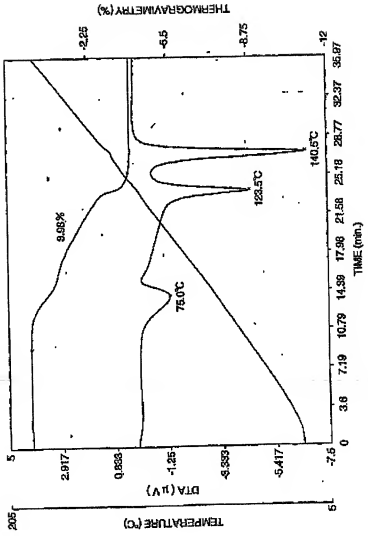
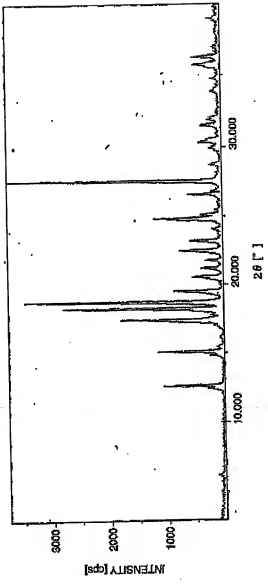
2500
2000
1500
1000
500
0
10.000
20.000
30.000
2θ [°]

[Figure 6]


THERMOGRAVIMETRY (%)
-2.25
-5.5
-8.75
-12
35.97
32.37
28.77
25.18
21.58
17.98
14.39
10.79
7.19
3.6
0
TIME (min.)
140.5°C
123.5°C
75.0°C
9.985%
TEMPERATURE (°C)
205
5
DTA (μV)
5
2.917
0.833
-1.25
-5.333
-9.417
-7.5

[Figure 7]



[DOCUMENT] Abstract

[Abstract]

[Problem] The problem of the present invention is provision of a pharmaceutical composition effective for treating mood disorders.

[Means for solving] The present inventive pharmaceutical composition comprises (1) aripiprazole and (2) a serotonin reuptake inhibitor. The serotonin reuptake inhibitor is those such as fluvoxamine, fluoxetine, paroxetine, sertraline, venlafaxine, milnacipran. By the co-use of (1) aripiprazole and (2) a serotonin reuptake inhibitor, mood disorders such as depression can effectively be treated.

[Selected drawing] None